

Reply to S. Zucker

We recently demonstrated that increased interleukin (IL)-6 production in Hodgkin's lymphoma is associated with an induction of hepcidin, which contributes to the iron-restricted anemia of chronic disease often observed at Hodgkin's lymphoma diagnosis.¹ Our data also suggested that increased hepcidin levels might not be sufficient for induction of anemia and that other mechanisms, possibly induced by IL-6, might be responsible. On the basis of well-founded reasoning, Zucker proposes in his letter that compensation by increased erythropoietin production may be the missing link to explain the lack of anemia, despite increased hepcidin levels.² Inappropriately high erythropoietin levels have been described as a compensation mechanism in hereditary spherocytosis with a reduced erythroid life span and without anemia.³ Zucker points out that IL-6 is a potential stimulator of erythropoietin as shown in a cell line model by Faquin et al.⁴ In this model, however, IL-6–induced erythropoietin stimulation was hypoxia-dependent and was not observed under normoxic conditions. In the tumor tissue, local hypoxia is present in a proportion of patients with Hodgkin's lymphoma, as suggested by necrotic areas resulting in the release of increased levels of circulating cell-free DNA.⁵ However, systemic hypoxia from anemia is considered the major stimulus for renal erythropoietin synthesis.

Applying the reasoning of Zucker to patients with Hodgkin's lymphoma, one would expect apparently inappropriate high erythropoietin levels in patients without anemia to compensate for the hepcidin-induced iron restriction. There are few data on erythropoietin levels in patients with Hodgkin's lymphoma at diagnosis. Pohl et al⁶ reported slightly, although not significant, higher serum erythropoietin levels in patients with nonanemic Hodgkin's lymphoma when compared with control, whereas erythropoietin levels in patients with anemia appeared to be adequate.

Zucker mentions the well-documented effect of erythropoietin on downregulation of hepcidin,^{7,8} even in the presence of inflammation,^{9,10} which indicates that erythropoietin trumps hepcidin as master regulator of erythropoiesis under conditions of inflammation. Continuing with this idea, one would expect that hepcidin levels should be lower than those observed in our patients without anemia. In conclusion, we agree that erythropoietin as a master regulator of erythropoiesis could probably be another player in the complex scenario of Hodgkin's lymphoma anemia, which may be the result of opposing effects between stimulators and inhibitors of erythropoiesis

and proteins involved in iron metabolism and iron-sensing pathways. The scenario remains open for other potential pathways to be defined.

Stefan Hohaus, Giuseppe Leone, Giuseppina Massini, Manuela Giachelia, and Barbara Vannata

Institute of Hematology, Catholic University S. Cuore, Rome, Italy

Luigi Maria Larocca

Institute of Pathological Anatomy, Catholic University S. Cuore, Rome, Italy

Maria Teresa Voso

Institute of Hematology, Catholic University S. Cuore, Rome, Italy

Dorine W. Swinkels

Laboratory Medicine, Radboud University, Nijmegen, the Netherlands

ACKNOWLEDGMENT

Supported by a grant from the Associazione Italiana per la Ricerca sul Cancro (Grant No. IG2007-4995).

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

REFERENCES

- Hohaus S, Massini G, Giachelia M, et al: Anemia in Hodgkin's lymphoma: The role of interleukin-6 and hepcidin. *J Clin Oncol* 28:2538-2543, 2010
- Zucker S: The swinging pendulum of the anemia of cancer: Erythropoietin trumps hepcidin. *J Clin Oncol* 29:e42, 2011
- Guarnone R, Centenara E, Zappa M, et al: Erythropoietin production and erythropoiesis in compensated and anaemic states of hereditary spherocytosis. *Br J Haematol* 92:150-154, 1996
- Faquin WC, Schneider TJ, Goldberg MA: Effect of inflammatory cytokines on hypoxia-induced erythropoietin production. *Blood* 79:1987-1994, 1992
- Hohaus S, Giachelia M, Massini G, et al: Cell-free circulating DNA in Hodgkin's and non-Hodgkin's lymphomas. *Ann Oncol* 20:1408-1413, 2009
- Pohl C, Schobert I, Moter A, et al: Serum erythropoietin levels in patients with Hodgkin's lymphoma at the time of diagnosis. *Ann Oncol* 3:172-173, 1992
- Nicolas G, Viatte L, Bennoun M, et al: Hepcidin, a new iron regulatory peptide. *Blood Cells Mol Dis* 29:327-335, 2002
- Ashby DR, Gale DP, Busbridge M, et al: Erythropoietin administration in humans causes a marked and prolonged reduction in circulating hepcidin. *Haematologica* 95:505-508, 2010
- Huang H, Constante M, Layoun A, et al: Contribution of STAT3 and SMAD4 pathways to the regulation of hepcidin by opposing stimuli. *Blood* 113:3593-3599, 2009
- Lasocki S, Millot S, Andrieu V, et al: Phlebotomies or erythropoietin injections allow mobilization of iron stores in a mouse model mimicking intensive care anemia. *Crit Care Med* 36:2388-2394, 2008

DOI: 10.1200/JCO.2010.32.3808; published online ahead of print at www.jco.org on November 15, 2010